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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,051	CAPLAN, MICHAEL J.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/4/03* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/24/05, 12/6/04, 10/25/04, 6/3/04, 2/2/04, 12/4/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 34-42 are pending.

2. Applicant's election without traverse of Group 12, claims 16-22 and 24-33 (now claims 34-42) drawn to a composition comprising dead E. coli containing therein at least one modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslink IgE as compared with the wild-type peanut allergen, filed 3/28/05, is acknowledged.

3. Claims 34-42, drawn to a composition comprising dead E. coli containing therein at least one modified peanut allergen whose amino acid sequence differs from that of a wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslink IgE as compared with the wild-type peanut allergen, are being acted upon in this Office Action.

4. Claim 34 is objected to under 37 CFR 1.821(d) because SEQ ID NO: is required.

5. Claims 35-37 are objected to because SEQ ID NO: 1-3 are polynucleotides, not proteins as recited in said claims.

6. The drawings, filed 12/4/03, are not approved. Figure legends of Figures 1-4 are poor. Margins of Figures 3 and 4 are not acceptable. Appropriate action is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising dead *E. coli.* containing therein at least one peanut allergen encoded by the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 2 and 3 (See page 33 of the specification), **does not** reasonably provide enablement for (1) any

composition comprising dead *E. coli*. containing therein at least one of any "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen such as wild-type peanut allergen is Ara h1 "(SEQ ID NO: 1)", wild-type peanut allergen is Ara h2 "(SEQ ID NO: 2)" or wild-type peanut allergen is Ara h3 "(SEQ ID NO: 3)" that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen, (2) any composition comprising dead *E. coli*. containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the modified peanut allergen differs from the sequence of any wild-type peanut allergen by one or more amino acid "deletions", "substitutions", or "additions" within any IgE binding site of any wild-type peanut allergen, (3) any composition comprising dead *E. coli*. containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the sequence of the modified peanut allergen "lacks" any "portion" of the wild-type peanut allergen sequence, and wherein said portion "includes" an IgE binding site, (4) any composition comprising dead *E. coli*. containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the modified peanut allergen is located in the cytoplasm or the periplasm of the dead *E. coli*, and (5) any composition comprising dead *E. coli*. containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the modified peanut allergen cannot be detected by antibody binding without disrupting the dead *E. coli* for a method of treating allergy in a subject susceptible to an anaphylactic allergic response to peanut. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a composition comprising heat killed *E coli*. containing therein at least one recombinant peanut allergen Ara h1 encoded by SEQ ID NO: 1, a recombinant peanut allergen Ara h2 encoded by SEQ ID NO: 2 or a recombinant peanut Ara h3 encoded by SEQ ID NO: 3 and a pharmaceutical acceptable carrier (page 31 of the specification). The specification further discloses a method of immunizing mice with said bacteria that produce said peanut allergens (page 34 of the specification). However, mice that have been immunized with the heat killed bacteria that makes Ara h1 fail to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

The specification does not teach how to make and use any composition comprising dead E coli containing any and all "modified peanut allergen" whose amino acid sequence differs from the sequence of the wild-type peanut allergen such as Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3 by one or more amino acid deletions, substitution, additions within which IgE binding site of said wild-type peanut allergen such that the allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type peanut allergen. There is insufficient guidance as to which amino acids corresponds to the IgE binding site to be modified by deletion, addition, substitution and combination thereof in Ara h1, Ara h2 and Ara h3, the corresponding nucleotides within the full length nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3 that can be deleted, substituted, added or combination thereof such that the resulting the modified peanut allergen has a reduced ability to bind to or cross-linked IgE in the claimed composition for treating peanut allergy. Further, there

is a lack of guidance as to the structure of the modified peanut allergen without the amino acid sequence. There is a lack of guidance as to which "portion" such as portion including an IgE binding site of the wild-type peanut allergen sequence is lacking in the modified peanut allergen without the amino acid sequence.

Burks et al (Eur. J Biochem 245(2): 334-9, April 1997; PTO 1449) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* (Arch Biochem Biophys 342(2): 244-53, June 1997; PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Given the unlimited number of modified peanut allergen, it is unpredictable which undisclosed modified peanut allergen in the claimed composition is effective for treating peanut allergy. Without the amino acid sequence of the modified peanut allergen, the cDNA encoding the corresponding modified allergen, one of skilled in the art cannot make the recombinant modified peanut allergen in E coli, much less for use in treatment of peanut allergy.

Chatel et al teach various factors such as the nature of the allergen, the mouse strain, the recombinant protein expressed influence the immune response to peanut allergen (see abstract, in particular). Chatel et al teach immune responses to proteins are known to be highly dependent on the nature of the allergen (see page 646, col. 1, first paragraph, in particular). Chatel et al teach immune response are also depends on the mouse strain (see page 646, col. 1, fourth paragraph, in particular).

Gottieb et al teach the immune system of mice is also quite different from that of man (see page 894, col. 3, in particular). Given the unlimited number of modified peanut allergens expressed in the dead E coli in the claimed composition, there is insufficient in vivo working example demonstrating the claimed composition is effective for treating peanut allergy.

Finally, immunizing mice with heat killed *E. coli* producing three different recombinant peanut allergens results in three different outcomes (see page 34 of instant specification). In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 34-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for (1) any composition comprising dead *E. coli.* containing therein at least one of any "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen such as wild-type peanut allergen is Ara h1 "(SEQ ID NO: 1)", wild-type peanut allergen is Ara h2 "(SEQ ID NO: 2)" or wild-type peanut allergen is Ara h3 "(SEQ ID NO: 3)" that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen, (2) any composition comprising dead *E. coli.* containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the

modified peanut allergen differs from the sequence of any wild-type peanut allergen by one or more amino acid "deletions", "substitutions", or "additions" within any IgE binding site of any wild-type peanut allergen, (3) any composition comprising dead *E. coli*. containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the sequence of the modified peanut allergen "lacks" any "portion" of the wild-type peanut allergen sequence, and wherein said portion "includes" an IgE binding site, (4) any composition comprising dead *E. coli*. containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the modified peanut allergen is located in the cytoplasm or the periplasm of the dead *E. coli*, and (5) any composition comprising dead *E. coli*. containing therein at least any one "modified peanut allergen" whose amino acid sequence differs from that of wild-type peanut allergen that occurs in nature such that the modified peanut allergen has a reduced ability to bind to or crosslinked IgE as compared with the wild-type peanut allergen wherein the modified peanut allergen cannot be detected by antibody binding without disrupting the dead *E. coli* for a method of treating allergy in a subject susceptible to an anaphylactic allergic response to peanut.

The specification discloses only a composition comprising heat killed *E coli*. containing therein at least one recombinant peanut allergen Ara h1 encoded by SEQ ID NO: 1, a recombinant peanut allergen Ara h2 encoded by SEQ ID NO: 2 or a recombinant peanut Ara h3 encoded by SEQ ID NO: 3 and a pharmaceutical acceptable carrier (page 31 of the specification). The specification further discloses a method of immunizing mice with said bacteria that produce said peanut allergens (page 34 of the specification). However, mice that have been immunized with the heat killed bacteria that makes Ara h1 fail to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally,

mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

Other than the specific composition mentioned above, there is inadequate written description about the structure associated with function of the "modified peanut allergen" in the claimed composition without the amino acid sequence, the corresponding cDNA encoding said modified peanut allergen containing therein in the dead *E coli* of the claimed composition. Further, the specification has not described the one or more amino acids within which IgE binding sites of Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3 to be deleted, substituted, added or combination thereof. Since the modified peanut allergen containing in the dead *E coli* of the claimed composition is not adequately described, it follows that the composition wherein the modified peanut allergen is located in the cytoplasm or the periplasm of the dead *E coli* are not adequately described. It also follows that the composition wherein the modified peanut allergen cannot be detected by any antibody binding without disrupting the dead E coli is not adequately described.

The specification discloses only dead E coli containing recombinant peanut allergen Ara h1 encoded by SEQ ID NO: 1, Ara h2 encoded by SEQ ID NO: 2 and Ara h3 encoded by SEQ ID NO: 3, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of modified peanut allergen containing in the dead *E coli* in the claimed composition to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 34-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "composition" in claim 34 as written reads on a compound, not a composition as claimed. Minimally, a composition comprising dead *E coli*... and a carrier is required.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 34, 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks et al (Int Arch Allergy Immunol: 118: 313-314, 1999; PTO 1449) in view of Evans et al (FEMS Microbil Immunol 1(3): 117-25, Dec 1998; PTO 892).

Burks et al teach a composition comprising *E coli* containing therein a modified peanut allergen such as modified Ara h2 wherein the modified peanut allergen differs from the wild-type peanut allergen by having more than one amino acid substitutions within the IgE binding epitopes 3, 4, 6, and 7 for alanine that has a reduced ability to bind IgE as compared with the wild-type peanut allergen (see page 313, col. 2, in particular). Burks et al teach modified peanut allergen Ara h2 may be useful as a safe efficacious immunotherapy for treatment of peanut allergy (see page 314, col. 1, in particular).

The invention in claim 34 differs from the teachings of the reference only in that the *E coli* is dead instead of live *E coli*.

Evans et al teach non-replicating dead *E coli* containing therein any desired antigen as a vaccine are efficient vehicle in terms of delivering antigens to the gut immune system (see abstract, in particular). Evans et al teach dead *E coli* can be obtained by treatment with chemical treatment such as Colicin E2 or heat treatment (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to heat killed *E coli* as taught by Evans with the *E coli* containing therein a modified peanut allergen such as modified Ara h2 as taught by Burks et al for a composition comprising dead *E. coli.* containing therein a modified peanut allergen such as modified Ara h2

as taught by Burks and Evans et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because non-replicating dead *E coli* containing therein any desired antigen is an efficient vehicle as a vaccine in terms of delivery of antigens to the gut immune system as taught by Evans et al. Burks et al teach modified peanut allergen Ara h2 may be useful as a safe efficacious immunotherapy for treatment of peanut allergy (see page 314, col. 1, in particular).

14. Claims 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks et al (Int Arch Allergy Immunol: 118: 313-314, 1999; PTO 1449) in view of Evans et al (FEMS Microbil Immunol 1(3): 117-25, Dec 1998; PTO 892) as applied to claims 34, 36 and 38 mentioned above and further in view of US Pat No. 5,888,799 (March 1999, PTO 1449) or Vrtala et al (J Clin Invest 99(7): 1673-1681, April 1997; PTO 892).

The combined teachings of Burks et al and Evans et al have been discussed supra.

The invention in claim 40 differs from the teachings of the references only in that the composition wherein modified peanut allergen is located in the cytoplasm of the dead *E coli*.

The invention in claim 41 differs from the teachings of the references only in that the composition wherein modified peanut allergen is located in the periphasm of the dead *E coli*.

The invention in claim 42 differs from the teachings of the references only in that the composition wherein modified peanut allergen cannot be detected by antibody binding without disrupting the dead *E coli*.

The '799 patent teaches a composition comprising *E. coli* K-12 (See Table in column 4, claims of '799, in particular) that produce allergen or portion thereof for treating allergy and the use of microorganisms such as *E coli* as a delivery vehicle (See column 6, lines 40-54, in particular). The '799 patent teaches it is possible to use a viable carrier incapable of reproduction that dies and releases cytoplasmic and/or perplasmic antigens (see col. 9, lines 24-26, in particular). The reference allergen is located within the periplasm (See column 14, lines 31-35, in particular). The reference microorganism such as *E. coli* K-12 have the advantages of (1) being avirulent (derivative of a pathogenic strain) and do not exchange genetic material with the pathogenic strains, (2) these microorganisms as a vaccine are capable of homing to, attaching to and invading or taking up by the gut associated lymphoid tissue (GALT), (3) carrying or

expressing on them the antigen or allergen of interest and (4) delivering the selected allergen to the GALT and thereby stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response (See column 2, lines 60-64, column 5, Table 1, in particular).

Vrtala et al teach *E coli* expressing recombinant nonanaphylactic birch pollen allergen wherein the reference allergen is the inclusion bodies located in the cytoplasm of the *E coli* (see page 1673, Methods, page 1674, col. 1, purification of recombinant Bet v1 (see page 1674, col. 1, third paragraph, in particular).

Therefore, it would have been have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the *E coli* containing therein a modified peanut allergen such as modified Ara h2 as taught by Burks et al for the *E coli* containing signal that directs the antigen to the periplasm as taught by the '779 patent or the *E coli* containing signal that directs the allergen to the cytoplasm as taught by Vrtala et al. The live *E coli* containing the modified peanut allergen located within the periplasm as taught by Burks et al and the '779 patent or within the cytoplasm as taught by Burks et al and Vrtala is then killed by heat treatment or chemical as taught by Evans et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because *E. coli* K-12 having allergen within the periplasm and/or cytoplasm as a vehicle carrying the allergen of interest is useful for treating allergy by delivering the pay load to the gut associated lymphoid tissue (GALT) and thereby stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response as taught by the '779 patent (See column 2, lines 60-64, column 5, Table 1, col. 9, line 24-26, in particular). Claim 42 is included in this rejection because modified peanut allergen that located in the inclusion bodies of the cytoplasm or periplasm would not be detect by antibody without disrupting the *E coli*. Non-replicating dead E coli containing therein any desired antigen is an efficient vehicle as a vaccine in terms of delivery of antigens to the gut immune system as taught by Evans et al. Burks et al teach modified peanut allergen Ara h2 may be useful as a safe efficacious immunotherapy for treatment of peanut allergy (see page 314, col. 1, in particular).

15. Claims 34-36, and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,486,311 (filed June 1998; PTO 892) in view of Evans et al (FEMS Microbil Immunol 1(3): 117-25, Dec 1998; PTO 892).

The '311 patent teaches a composition comprising live *E coli* (see col. 7, line 41, in particular) containing therein at least one peanut allergen such as Ara h 1 that has the identical nucleic acid as the claimed SEQ ID NO: 1 (see reference SEQ ID NO: 17, Table 19, in particular), and Ara h2 that has the same nucleic acid as the claimed SEQ ID NO: 2 (see reference SEQ ID NO: 21, in particular) and a method of producing the same (see col. 7, line 39-53, in particular). The '311 patent teaches various modified peanut allergen such as Ara h1 wherein at least one or more amino acid within the IgE binding sites have been substituted (see Figure 5, col. 13, line 21-51, in particular). The '311 patent further teaches various modified peanut allergen such as Ara h2 wherein at least one or more amino acid within the IgE binding sites have been substituted (see col. 28, Table 10, col. 29, line 16-2, in particular).

The invention differs from the teachings of the reference only in that the *E coli* is dead instead of live *E coli*.

Evans et al teach non-replicating dead *E coli* containing therein any desired antigen as a vaccine are efficient vehicle in terms of delivering antigens to the gut immune system (see abstract, in particular). Evans et al teach dead *E coli* can be obtained by treatment with chemical treatment such as Colicin E2 or heat treatment (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make any *E coli* containing any modified Ara h1 and Ara h2 wherein one or more amino acid within the IgE binding sites have been substituted or deleted for a composition as taught by the '177 patent and then heat killed *E coli* as taught by Evans. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because non-replicating dead *E coli* containing therein any desired antigen is an efficient vehicle as a vaccine in terms of delivery of antigens to the gut immune system as taught by Evans et al. The '311 patent teaches modified peanut allergens such as Ara h1 and Ara h2 have reduced ability to bind IgE as compared with wild-type peanut allergen and may be useful as a safe efficacious immunotherapy for treatment of peanut allergy (see page col. 7, lines 57-62, in particular).

16. Claims 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,486,311 (filed June 1998; PTO 892) in view of Evans et al (FEMS Microbil Immunol 1(3): 117-25, Dec 1998; PTO 892) as applied to claims 34-36, and 38-39 and further in view of US Pat No. 5,888,799 (March 1999, PTO 1449) or Vrtala et al (J Clin Invest 99(7): 1673-1681, April 1997; PTO 892).

The combined teachings of the '311 patent and Evans et al have been discussed supra.

The invention in claim 40 differs from the teachings of the references only in that the composition wherein modified peanut allergen is located in the cytoplasm of the dead *E coli*.

The invention in claim 41 differs from the teachings of the references only in that the composition wherein modified peanut allergen is located in the periphasm of the dead *E coli*.

The invention in claim 42 differs from the teachings of the references only in that the composition wherein modified peanut allergen cannot be detected by antibody binding without disrupting the dead *E coli*.

The '799 patent teaches a composition comprising *E. coli* K-12 (See Table in column 4, claims of '799, in particular) that produce allergen or portion thereof for treating allergy and the use of microorganisms such as *E coli* as a delivery vehicle (See column 6, lines 40-54, in particular). The '799 patent teaches it is possible to use a viable carrier incapable of reproduction that dies and releases cytoplasmic and/or perplasmic antigens (see col. 9, lines 24-26, in particular). The reference allergen is located within the periplasm (See column 14, lines 31-35, in particular). The reference microorganism such as *E. coli* K-12 have the advantages of (1) being avirulent (derivative of a pathogenic strain) and do not exchange genetic material with the pathogenic strains, (2) these microorganisms as a vaccine are capable of homing to, attaching to and invading or taking up by the gut associated lymphoid tissue (GALT), (3) carrying or expressing on them the antigen or allergen of interest and (4) delivering the selected allergen to the GALT and thereby stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response (See column 2, lines 60-64, column 5, Table 1, in particular).

Vrtala et al teach *E coli* expressing recombinant nonanaphylactic birch pollen allergen wherein the reference allergen is the inclusion bodies located in the cytoplasm of the *E coli* (see page 1673, Methods, page 1674, col. 1, purification of recombinant Bet v1 (see page 1674, col. 1, third paragraph, in particular).

Therefore, it would have been have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the *E coli* containing therein a modified peanut allergen such as modified Ara h1 or Ara h2 as taught by the '311 patent for the *E coli* that containing signal that directs the allergen to the periplasm and/or cytoplasm as taught by the '779 patent or the *E coli* containing signal that directs the allergen to the cytoplasm as taught by Vrtala et al. The live *E coli* containing the modified peanut allergen located within the periplasm or cytoplasm is then killed by heat treatment or chemical as taught by Evans et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because *E. coli* K-12 having allergen within the periplasm and/or cytoplasm as a vehicle carrying the allergen of interest is useful for treating allergy by delivering the pay load to the gut associated lymphoid tissue (GALT) and thereby stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response as taught by the '779 patent (See column 2, lines 60-64, column 5, Table 1, col. 9, line 24-26, in particular). Claim 42 is included in this rejection because modified peanut allergen that located in the inclusion bodies of the cytoplasm or periplasm would not be detect by antibody without disrupting the E coli. Non-replicating dead *E coli* containing therein any desired antigen is an efficient vehicle as a vaccine in terms of delivery of antigens to the gut immune system as taught by Evans et al. Burks et al teach modified peanut allergen Ara h2 may be useful as a safe efficacious immunotherapy for treatment of peanut allergy (see page 314, col. 1, in particular).

17. Claims 34 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabjohn et al (J Clin Invest 103(4): 535-542, Feb 1999; PTO 1449) in view of Evans et al (FEMS Microbil Immunol 1(3): 117-25, Dec 1998; PTO 892).

Rabjohn et al teach a composition comprising the *E coli* (see page 536, col. 2, Bacterial Expression and purification recombinant Ara h3, in particular) containing therein a modified peanut allergen such as modified Ara h3 wherein the modified peanut allergen differs from the wild-type peanut allergen by having more than one amino acid substitutions within the IgE binding epitopes 1-4 for alanine that has a reduced ability to bind IgE as compared with the wild-type peanut allergen (see page 540, Table 2, Figure 5, in particular). The reference wild type

peanut allergen Ara h3 has the same sequence as that of claimed SEQ ID NO: 3 (see page 537, Fig. 1, in particular). Rabjohn et al teach the cDNA encoding the modified peanut allergen Ara h3 is useful for treating peanut allergy (see paragraph bridging page 541-2, in particular).

The invention differs from the teachings of the reference only in that the *E coli* is dead instead of live *E coli*.

Evans et al teach non-replicating dead *E coli* containing therein any desired antigen as a vaccine are efficient vehicle in terms of delivering antigens to the gut immune system (see abstract, in particular). Evans et al teach dead *E coli* can be obtained by treatment with chemical treatment such as Colicin E2 or heat treatment (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to killed *E coli* as taught by Evans with the *E coli* containing therein a modified peanut allergen such as modified Ara h3 as taught by Rabjohn et al for a composition comprising dead *E. Coli* containing therein a modified peanut allergen such as modified Ara h3 as taught by Rabjohn et al and Evans et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because non-replicating dead *E coli* containing therein any desired antigen is an efficient vehicle as a vaccine in terms of delivery of antigens to the gut immune system as taught by Evans et al. Rabjohn et al teach the cDNA encoding the modified peanut allergen Ara h3 is useful for treating peanut allergy (see paragraph bridging page 541-2, in particular).

18. Claims 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabjohn et al (J Clin Invest 103(4): 535-542, Feb 1999; PTO 1449) in view of Evans et al (FEMS Microbil Immunol 1(3): 117-25, Dec 1998; PTO 892) as applied to claims 34 and 37-39 mentioned above and further in view of and further in view of US Pat No. 5,888,799 (March 1999, PTO 1449) or Vrtala et al (J Clin Invest 99(7): 1673-1681, April 1997; PTO 892).

The combined teachings of the Rabjohn et al and Evans et al have been discussed supra.

The invention in claim 40 differs from the teachings of the references only in that the composition wherein modified peanut allergen is located in the cytoplasm of the dead *E coli*.

The invention in claim 41 differs from the teachings of the references only in that the composition wherein modified peanut allergen is located in the periphasm of the dead *E coli*.

The invention in claim 42 differs from the teachings of the references only in that the composition wherein modified peanut allergen cannot be detected by antibody binding without disrupting the dead *E coli*.

The '799 patent teaches a composition comprising *E. coli* K-12 (See Table in column 4, claims of '799, in particular) that produce allergen or portion thereof for treating allergy and the use of microorganisms such as *E coli* as a delivery vehicle (See column 6, lines 40-54, in particular). The '799 patent teaches it is possible to use a viable carrier incapable of reproduction that dies and releases cytoplasmic and/or perplasmic antigens (see col. 9, lines 24-26, in particular). The reference allergen is located within the periplasm (See column 14, lines 31-35, in particular). The reference microorganism such as *E. coli* K-12 have the advantages of (1) being avirulent (derivative of a pathogenic strain) and do not exchange genetic material with the pathogenic strains, (2) these microorganisms as a vaccine are capable of homing to, attaching to and invading or taking up by the gut associated lymphoid tissue (GALT), (3) carrying or expressing on them the antigen or allergen of interest and (4) delivering the selected allergen to the GALT and thereby stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response (See column 2, lines 60-64, column 5, Table 1, in particular).

Vrtala et al teach *E coli* expressing recombinant nonanaphylactic birch pollen allergen wherein the reference allergen is the inclusion bodies located in the cytoplasm of the *E coli* (see page 1673, Methods, page 1674, col. 1, purification of recombinant Bet v1 (see page 1674, col. 1, third paragraph, in particular).

Therefore, it would have been have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the *E coli* containing therein a modified peanut allergen such as modified Ara h3 as taught by Rabjohn et al for the *E coli* containing signal that directs the antigen to the periplasm and/or cytoplasm as taught by the '779 patent or the *E coli* containing signal that directs the allergen to the cytoplasm as taught by Vrtala et al. The live *E coli* containing the modified peanut allergen Ara h3 located within the periplasm or cytoplasm is then killed by heat treatment or chemical as taught by Evans et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because *E. coli* K-12 having allergen within the periplasm and/or cytoplasm

as a vehicle carrying the allergen of interest is useful for treating allergy by delivering the pay load to the gut associated lymphoid tissue (GALT) and thereby stimulating the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response as taught by the '779 patent (See column 2, lines 60-64, column 5, Table 1, col. 9, line 24-26, in particular). Claim 42 is included in this rejection because modified peanut allergen that located in the inclusion bodies of the cytoplasm or periplasm would not be detect by antibody without disrupting the *E coli*. Non-replicating dead *E coli* containing therein any desired antigen is an efficient vehicle as a vaccine for delivering antigens to the gut immune system as taught by Evans et al. Rabjohn et al teach the cDNA encoding the modified peanut allergen Ara h3 is useful for treating peanut allergy (see paragraph bridging page 541-2, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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